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1. Your reference	W072122PGB	
2. Patent application number *(The Patent Office will fill in this part)*	0311846.0	23 MAY 2003
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	The University of Birmingham Edgbaston Birmingham B15 2TT	
Patents ADP number *(if you know it)*	798165002	
If the applicant is a corporate body, give the country/state of its incorporation	England	
4. Title of the invention	HIGH STRENGTH AND INJECTABLE APATITIC CALCIUM PHOSPHATE CEMENTS	
5. Name of your agent *(if you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Marks & Clerk Alpha Tower Suffolk Street Queensway Birmingham B1 1TT England	
Patents ADP number *(if you know it)*	18002	

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Continuation sheets of this form	
Description	17
Claim *(s)*	
Abstract	
Drawing *(s)*	1 + 1

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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
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11. I/We request the grant of a patent on the basis of this application.

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Date 22 MAY 2001

12. Name and daytime telephone number of person to contact in the United Kingdom

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Improved Calcium Phosphate Cements

The present invention relates to an improved self-setting calcium phosphate cement which is injectable and mechanically strong when set.

Clinically, the main application of self-setting calcium phosphate cements (CPC) is currently in cranio-and maxillofacial surgery for the reconstruction of bone defects, due to their ease of use, clinical performance and conformability. The location of these defect sites is chosen so that little loading of the implant occurs, since these materials are both weak and brittle compared to the bone they replace. Compressive strengths of CPC reported in literature are in the range of 20 – 83 MPa, dependent on the composition and pre-treatment of the materials, while the strengths of cortical bone is up to about 170 MPa. A broadening of the indications for which CPC can be used, for example in the field of upper spine surgery (vertebroplasty), may require a higher strength material. Additionally a cement paste that had high strength in addition to being of sufficiently low viscosity as to be applied by minimal invasive injectable materials, would further widen applications to include indications not freely accessible by open surgery. Presently only polymeric materials, like PMMA bone cements fulfil these requirements (compressive strengths of about 65-100 MPa and tensile strengths of 25-50 MPa) but their setting exotherm and monomer toxicity are barriers to their use near the central nervous system.

Often when unmodified CPC, consisting only of calcium phosphate particles and water containing dissolved phosphate/hydrogen phosphate ions as liquid phase, is delivered through a narrow bore needle or cannula, a filter-pressing phenomena can occur leading to a phase separation of liquid and solid phase.

Injectable cements can be obtained by decreasing the powder to liquid ratio (P/L ratio), but this has a detrimental effect on the mechanical properties due to a higher porosity of the hardened cement matrix. In an attempt to improve rheological properties, the influence of several additives to the liquid phase, such as: lactic acid, glycerol, chitosan, citric acid or soluble polymers, on the injectability of calcium phosphate cements has been studied by several authors (Leroux L, et. al.: Effects of various adjuvants (lactic acid, glycerol and chitosan) on the injectability of a calcium phosphate cement. Bone 1999; 25(2): 31-34. and Ginebra MP, et. al.: Mechanical and rheological improvement of a calcium phosphate cement by the addition of a polymeric drug. J Biomed Mater Res 2001; 57(1): 113-118).

Because of the biocompatibility of citrate ions, which are present in bone, several authors have investigated the influence of citric acid on the properties of calcium phosphate cements and the reaction kinetics of hydroxyapatite formation (Sarda S, et. al.: Kinetic effect of citric acid influence on calcium phosphate bone cements as water reducing agent, J Biomed Mater Res 61: 652-659, 2002). Citric acid retards the formation of hydroxyapatite as was shown for phase pure α-TCP as well as for TTCP /DCPD cement systems. The setting reaction to HA is retarded, probably because of adsorption of the citrate ions onto both reactant and product phases and a low pH value of the cement paste during hardening. In contrast to acetate ions, the level of supersaturation, necessary for precipitation of HA from the liquid increases in the presence of citrate ions from 10.93 to 11.73 (Van der Houwen, JAM, et al.: The application of calcium phosphate precipitation chemistry to phosphorous recovery: the influence of organic ligands, Environmental Technology, 2001; 22: 1325-1335). In some cases, citric acid has been shown to increase the injectability of cement

pastes at lower levels of the acid but significant gains in strength have not been reported as a consequence of the reduced water content of these formulations.

It is an object of the present invention to provide an improved self setting calcium phosphate cement which preferably has improved mechanical properties when set and which is preferably of sufficiently low viscosity to be injectable.

According to the present invention there is provided a self setting calcium phosphate cement comprising:-

(i) a powdered component, said powdered component having an average particle size d_{50} of less than 15 μm, and

(ii) a calcium phosphate based powder, said powder having an average particle size d_{50} greater than that of the powdered component,

said powdered component and said calcium phosphate based powder being suspended in water containing a dissolved zeta potential increasing additive in sufficient quantity to increase the zeta potential of the suspended particles to at least 30 mV, and wherein the zeta potential increasing additive is chosen to be compatible with the setting pH of the same calcium phosphate cement without the zeta potential increasing additive.

Preferably, the d_{50} of the calcium phosphate based powder is from about 1.5 to about 10 times greater than the d_{50} of the powdered component.

Preferably, the zeta potential increasing additive is an oligocarboxylic acid compound.

It will be understood that certain calcium phosphate based cements set at an approximately neutral pH, in which case the oligocarboxylic acid compound is an appropriate salt of the carboxylic acid. Suitable salts include group I or group II metal salts (e.g. sodium, potassium or calcium), ammonium salts and mixed salts. Other calcium phosphate based cements set at acidic pH, in which case the oligocarboxylic acid compound is the oligocarboxylic acid itself.

Preferably, said oligocarboxylic acid compound has two or three carboxyl groups. Preferably, said oligocarboxylic acid compound has one or more hydroxyl groups.

Preferred oligocarboxylic acids compounds are citric acid, tartaric acid and malic acid, and their salts, with trisodium citrate and disodium tartrate being particularly preferred for neutral setting cements.

Preferably, the zeta potential increasing additive is in sufficient quantity to increase the zeta potential of the calcium phosphate particles to at least 40 and preferably at least 50mV.

Preferably, the zeta potential increasing additive is present in an amount of from 0.01 to 2 Mol per litre of water, more preferably 0.1 to 1 Mol per litre and most preferably 0.2 to 1 M per litre.

Preferably, the powdered component has a d_{50} of no more than10 μm, more preferably no more than 5 μm and possibly as low as 1 μm or less. The powdered component may be calcium phosphate based, for example it may be calcium phosphate, dicalcium phosphate anhydride, dicalcium phosphate dihydrate α-tricalcium phosphate, β-tricalcium phosphate, tetracalcium

phosphate, hydroxyapatite, or octacalcium phosphate or substituted (eg. potassium, silicon, sodium, carbonate, sulphate etc.) forms thereof. Alternatively, the powdered component may be any other biocompatible ceramic material such as calcium carbonate, calcium sulphate, zirconium oxide or titanium oxide or mixtures thereof.

Preferably, the calcium phosphate based material has a d_{50} of at least 3 μm. Preferably, the calcium phosphate based material (which may be in any convenient state for example crystalline, nanocrystalline, amorphous or mechanically activated) is tetracalcium phosphate, α- or β-tricalcium phosphate, hydroxyapatite, monocalcium phosphate monohydrate, monocalcium phosphate anhydrous or mixtures thereof.

Preferably, the volume ratio of the calcium phosphate based powder to the powdered component is in the range of from 60:40 to 95:5.

The inventors have discovered that the combination of the bimodal particle distribution and the presence of the zeta potential increasing compound have a considerable effect on the viscosity of the resulting calcium phosphate cement. As such, much higher powder to liquid ratios can be achieved whilst maintaining injectability of the cement.

Furthermore, the cements of the present invention may be re-moulded or shaped after pre-compression, to give either high strength cements which can be applied clinically in the absence of applied pressure, or high strength near-net-shape implants.

The present invention will be further described by way of example, with reference to the accompanying drawing which is a plot of applied force against displacement to show injectability of various cement compositions.

CPC can be considered as a high viscosity ceramic powder suspension. The basic principle of the present invention is the adjustment of a surface charge of the cement particle surface in the liquid phase (zeta-potential). A high zeta-potential improves the dispersion of the fine particles in the micron to sub-micron range as a result of the mutual repulsion of particles in the liquid phase and minimizes therefore the attractive interparticulate forces. For cements with a bimodal particle size distribution as claimed, the high surface charge of the particles allows the de-agglomeration of the fine particles in the liquid phase. These de-agglomerated fine particles can then fill the space between a dense packing of the coarser particles, minimizing the required liquid for cement paste formation and the resulting porosity and therefore maximizing the mechanical strength of the hardened cement matrix. Zeta- potential may be altered by adding multiple charged ions to the liquid phase, which can lead to an increase of the charge density of the particle surface by adsorption on the solid / liquid interface. The main requirements for additives to CPC for implantation are non-toxicity as well as lack of detrimental effect on mechanical properties e.g. due to excessive inhibition of the cement setting reaction. Particularly useful additives for increasing the zeta-potential within CPC are sodium (and calcium) salts of citric acid.

A. TTCP/DCPA cement

Cement preparation: TTCP (tetracalcium phosphate) was prepared by sintering an equimolar mixture of DCPA (dicalcium phosphate anhydride) (Baker) and

calcium carbonate (Baker) at 1500°C for 18h followed by quenching in air, followed by milling in agate jars to a d_{50} of 15 μm. DCPA was milled in 96% ethanol by means of a ball mill for 24h to a d_{50} of 0.7 μm. TTCP and DCPA were mixed at a nearly equimolar ratio (0.91), weight ratio 7:3 in a ball mill for 1h. 0.97 weight% of dry sodium phosphate accelerator was mixed with the cement to adjust the initial setting time according to the Gilmore-needle test to about 5min at 37°C.

Specimen Preparation: Cement cylinders with an aspect ratio of 2:1 (6mm diameter x12mm length) were fabricated with powder to liquid mass ratios of between 2.7 – 5. The cement pastes were biaxially compressed up to 200 MPa for 5 s. The specimens were removed from the moulds after 2h setting and stored in water at 37°C for an additional 22h prior to testing.

***Compressive testing*:** Strengths (n=6) were measured at a crosshead speed of 1mm/min using a static mechanical testing machine *Zwick 1440* (Zwick, Ulm, Germany) with a 5 kN load cell. Samples with strengths over 160MPa were tested on an Instron 1185 with a 100kN load cell.

Injectability

10 g of CPC powder were mixed with water or 500mM trisodium citrate solution at PLR mass ratios of between 3.3 and 5 on a glass slab. The cement paste was transferred into a 10ml syringe by means of a spatula. The paste was extruded through a 1.1mm x 30mm needle using a mechanical testing machine (*Zwick 1440*) at cross-head speed of 20 mm/min and a maximum force of 300 N. This force was selected since this was determined to be the maximum force that could be applied manually.

Comparative examples

The liquid phase was either water, an aqueous solution of citric acid (500 mM) or an aqueous solution of sodium acetate.

Examples

The liquid phase was an aqueous solution of trisodium citrate at concentrations of 100 mM to 1 M, or disodium tartrate at a concentration of 500 mM).

1. Trisodium citrate containing solutions

The compressive strengths of the cement samples are tabulated in Table 1 below. At a P/L ratio of 3.3 it can be seen that the values for the trisodium citrate samples are higher than for the comparative water and citric acid samples. The effect is even more marked at higher levels of sodium citrate, with the strengths being 50-60% higher at 500 mM trisodium citrate. The effect can be explained mechanistically by a decrease of the porosity of the hardened cement matrix.

Table 1.

Liquid	Compressive strength [MPa]		
	P/L = 3.3	P/L = 4	P/L = 5
water	62.5 ± 5.0	51.6 ± 11.3	30.1 ± 10.7
100mM Na_3citrate	77.3 ± 8.4	78.9 ± 9.7	77.1 ± 7.2
200mM Na_3citrate	87.4 ± 11.7	90.0 ± 6.6	93.4 ± 9.6
500mM Na_3citrate	102.4 ± 7.5	108.7 ± 18.7	108.8 ± 13.0
750mM Na_3Citrate	101.2 ± 13.3	-	-
1M Na_3Citrate	98.9 ± 14.0	-	-
500mM Citric Acid	67.1 ± 9.3	-	26.2 ± 6.1

As might be expected, as the P/L ratio increases, the strengths of the water and citric acid cements decreases, primary due to the difficulty in mixing such a dry paste causing poor sample quality. In contrast, the strength of the trisodium citrate samples was relatively insensitive to the P/L ratio.

Furthermore, the use of trisodium citrate solutions as liquid phase in different concentrations (0.1 – 1mol/l) results in a decrease of the macroscopically observable viscosity of the cement paste and therefore permits improved injectability.

Referring to the drawing, injectability of cements mixed with 0.5M trisodium citrate solution (P/L of 3.3) were compared with injectability of cements having water or citric acid (0.5M) as the liquid phase. The applied force increased at the beginning of the injection and reached a constant level after several mm displacement of the syringe, disrupted only in part by a sudden decrease of the pressure when air bubbles were pressed out through the needle. After about 25-30 mm displacement the applied forces strongly increase up to the limit of 300N since no further paste remained in the syringe. In contrast, water and 0.5M citric acid solution containing pastes only had injectabilities of 60% and 13% respectively (P/L 3.3, max force 300N). For both liquids a continuous increase of the injection forces were obtained. The applied forces for injecting cement pastes with sodium citrate solution increase with cross-head speed; an average speed of 20mm/min (about 90s for injecting the whole cement paste) requires a force of 22-24 N at P/L = 3.3 compared to 60 N at a speed of 50mm/min. Higher P/L mixes (up to 4.5) were still injectable (>90%), but required higher forces, typically 90-120 N.

The reason for the observable effects of an increased injectability and a mechanical reinforcement is the highly charged particle surface (zeta-potential) of the calcium phosphate particle when trisodium citrate is used as liquid. The zeta-potentials of DCPA and TTCP has been reported previously as −15 mV (TTCP) and −18 mV (DCPA) in pure water. Using trisodium citrate solution the particle surfaces were highly charged due to the adsorption of citrate ions with zeta-potentials of about −50 to −55 mV. This increase of the zeta-potential leads to a much lower viscosity of the cement paste due to a decrease of the attractive interparticulate forces by an electrostatic mutual repulsion of the particles in combination with a bimodal particle size distribution of the cement.

HA cement mixed with water, sodium citrate and citric acid solutions (P/L ratio 3.3) were compacted at 2.7, 9.0, 36, 50 and 200 MPa. Compressive strength, density and phase composition were determined after storage in water at 37°C after 24 hours. Table 2 shows the effect of compaction pressure and liquid composition on the mechanical properties and degree of conversion of cements mixed at a P:L ratio of 3.3.

Table 2

Liquid	Compaction Pressure (MPa)	Compressive Strength (MPa)	wt% HA
Water	2.7	62.5 ± 5.0	79.96
Water	9	83.4 ± 11.4	74.84
Water	36	106.8 ± 11.0	72.37
Water	50	113.2 ± 16.0	77.93
Water	200	118 ± 16.0	27.58
100mM Na_3C	2.7	77.3 ± 8.4	77.19
200mM Na_3C	2.7	87.4 ± 11.7	76.6
500mM Na_3C	2.7	102.40±7.5	78.67
500mM Na_3C	9	131.3 ± 8.8	78.47
500mM Na_3C	36	154.4 ± 14.4	78.45
500mM Na_3C	50	153.6 ± 19.3	73.58
500mM Na_3C	200	184.0 ± 19.3	38.62
500mM CA	2.7	22.3 +/- 6.4	61.49
(48 hrs)		67.1 +/- 9.3	(66.67)
500mM CA	9	21.0 +/- 3.6	67.59
(48 hrs)		86.9 +/- 11.1	77.50
500mM CA	50	29.4 +/- 4.3	72.13
(48 hrs)		115.9 +/- 9.7	80.72

CA=citric acid, Na_3C=trisodium citrate

It was found that by compacting cements made with sodium citrate biaxially to 200MPa, very high strength materials were produced (184 MPa) despite the extent of reaction being limited, whereas water and citric acid only yielded cements with 116-118MPa. After 24hr setting cement made with citric acid was initially very weak (20-30MPa) and this increased after a further 24 hours to similar levels achieved using water.

In order to determine whether this effect might have any clinical benefit, cement mixes, (powder: liquid ratio 3.3 g/ml) containing either water, 500mM citric acid

or sodium citrate that were manually pressed into cylindrical moulds under finger pressure, (estimated from load cell measurements to be ~ 1.5 MPa) were investigated. The use of sodium citrate had a remarkable strength improvement effect over the use of water (101.2 ± 13.7 and 33.1 ± 11.9MPa respectively). The low and variable strengths of the water mixed cements was as a result of poor specimen quality due to difficulties in handling and compacting the thick paste, sodium citrate containing mixes however were a viscous liquid. While finger pressure may seem insignificant, even 700kPa which equates to 7kg force per cm^2 is too high for use in delicate tissues and in uncontained bone defects where the cement paste would simply flow away from the applied force. In order to determine whether high strength near net shape cement implants could be made by pre-compaction, rectangular prisms (aspect ratio 2:1) were cut with a scalpel from unset cement cylinders made with 500mM sodium citrate compacted to 2.7MPa. After 24 hours they were found to have wet compressive strengths of 97.4 ± 8.6 MPa. In order to determine whether a mouldable system could be generated, the same cement formulation was compacted to 2MPa and removed from the die. The cement paste was then transferred into cylindrical moulds by spatula and allowed to set before removal and storage in water for 24 hours. These cements had wet compressive strengths of 88.6 ± 6.3 MPa. This demonstrates the potential of using a precompaction stage in a delivery system of sodium citrate containing CPC to generate high strength cement pastes that can be applied clinically in the absence of applied pressure.

By using a compaction pressure of 200MPa it was possible to fabricate cements with a mean wet strength in excess of 180MPa. This is near to the upper strength range of cortical bone and demonstrates that this cement system, contrary to current thinking, may be capable of being used in some load bearing applications.

Even without precompaction, strength values are higher using sodium citrate (500 mM) than using water (Table 3). Furthermore, the lowering of viscosity enables higher workable P/L ratios to be obtained.

Table 3

	P/L					
	2.0	2.7	3.3	4.0	4.5	5.0
0.5M sodium citrate	8.7 ± 0.7	28.1 ± 1.2	36.1 ± 4.1	50.5 ± 6.0	57.7 ± 10.8	67.1 ± 6.1
water	4.8 ± 1.2	-	17.6 ± 2.87	UNWORKABLE		

High strength calcium phosphate cements are also of interest in the manufacture of macroporous scaffolds for use as tissue engineering scaffolds and preformed bone grafts. Macroscale pores (>300μm) allow the ingrowth of blood vessels and hence the formation of new bone but can reduce the strength of a cement by an order of magnitude, rendering most cements extremely fragile. It would appear from analogy with previous reports (J.E. Barralet, et. al., *Biomaterials* **2002,** *23,* 3063) that porous cements could be made with strengths within the compressive strength range of human cancellous bone (~1.5 - 45MPa) using this system.

2. Disodium tartrate containing solutions

The scope of the invention was further explored by making TTCP/DCPA cements (as described above) using a disodium tartrate solution (500 mM) instead of trisodium citrate. A similar strength sodium acetate solution was used for comparison.

The effective surface charges of the TTCP, DCPA and precipitated HA particles in contact with an aqueous electrolyte were determined from zeta-potential measurement. Analysis was performed on a Zeta-Sizer 3000 (Malvern Instruments) in double distilled water and various 50mM electrolytes. Measurements were performed 10 times and the average potential and the standard deviation were calculated.

As can be seen from Table 4 below, the zeta potentials obtained for the starting calcium phosphates and the resultant hydroxyapatite using disodium tartrate were significantly higher than when using sodium acetate.

Table 4: Zeta-Potentials of cement components (TTCP, DCPA) in different electrolytes (0.05mol/l)

	Zeta-Potential [mV]	
	Na_2Tartrate	NaAcetate
DCPA	-41.7+/- 2.1	-35.4 +/- 0.7
TTCP	-40.9 +/- 2.2	-28.9 +/- 2.6
HA precip.	-40.5 +/- 1.4	-13.3 +/- 1.7

Compressive strengths were measured (after 24hrs setting at 37°C following pre-compression at 2.7 MPa). As can be seen in Table 5 below, the disodium tartrate gave significantly greater (more than double) strength values than sodium acetate.

Table 5: Mechanical strengths of TTCP/DCPA cement at various P/L ratios and different compositions of the liquid phase

Liquid	Compressive strength [MPa]	
	P/L = 3.3	P/L = 4
0.5 mol/l NaAcetate	45.7 +/- 3.9	42.8 +/- 5.7
0.5 mol/l Na_2Tartrate	96.4 +/- 10.2	86.9 +/- 8.4

B. Mechanically activated α-Tricalcium Phosphate Cements (MaαT)

Cement Preparation

α-TCP was dry ball milled for 4 hours or for 1 hour in ethanol to give a mechanically activated powder having a d_{50} of 7.1μm or 6.99μm respectively. The other cement components were added and mixed in a coffee grinder for approximately 20 to 30 seconds. Specimen preparation and compressive strength testing was carried out as described above (pre-compression of samples was at 9 MPa).

The results are shown in Table 6 below, from which it can be seen that the incorporation of DCPA or MaβT to provide a bimodal particle distribution and trisodium citrate to increase the zeta potential resulted in a cement having a higher compressive strength.

Table 6 Compressive strengths of MaαT

Composition	Liquid	P/L	CS [MPa]
MaT[1]	2.5 Na_2HPO_4	2.5	82.0 +/- 8.3
MaαT[1], 15% DCPA (0.7μm)	0.5M Na_3citrate 2.5 Na_2HPO_4	4.0	114.0 +/- 15.3
MaαT[1], 30% DCPA (0.7μm)	0.5M Na_3citrate 2.5 Na_2HPO_4	4.0	114.5 +/- 26.7
MaαT[2]	2.5 Na_2HPO_4	2.5	74.5+/-13.6
MaαT[2], 30% MaβT[3]	0.5M Na_3citrate 2.5 Na_2HPO_4	3.6	93.3+/-16.1

[1] Dry ground for 4 hours (d_{50} 7.1μm)

[2] Wet ground for 1hour (d_{50} 6.99μm)

[3] MaβT=mechanically activated β-TCP, wet ground in ethanol to give a powder having a d_{50} of 3μm.

C. Acidic setting cement

Cement Preparation

ß-Tricalcium phosphate was prepared by heating a mixture of dicalcium phosphate anhydride (DCPA, Baker) and calcium carbonate (CC, Merck) in a molar ratio of 2:1 up to 1050°C for 24h, followed by quenching to room temperature. The sintered cake was crushed with pestle and mortar and sieved until it passed through a 355μm sieve. The material was ground in a ball mill to a medium particle size d_{50} of 9.8 μm. Monocalcium phosphate monohydrate with a medium particle size d_{50} of 23.3 μm was purchased from Baker and used as received. Both materials were mixed in equimolar amounts in a coffee grinder for approximately 20-30s.

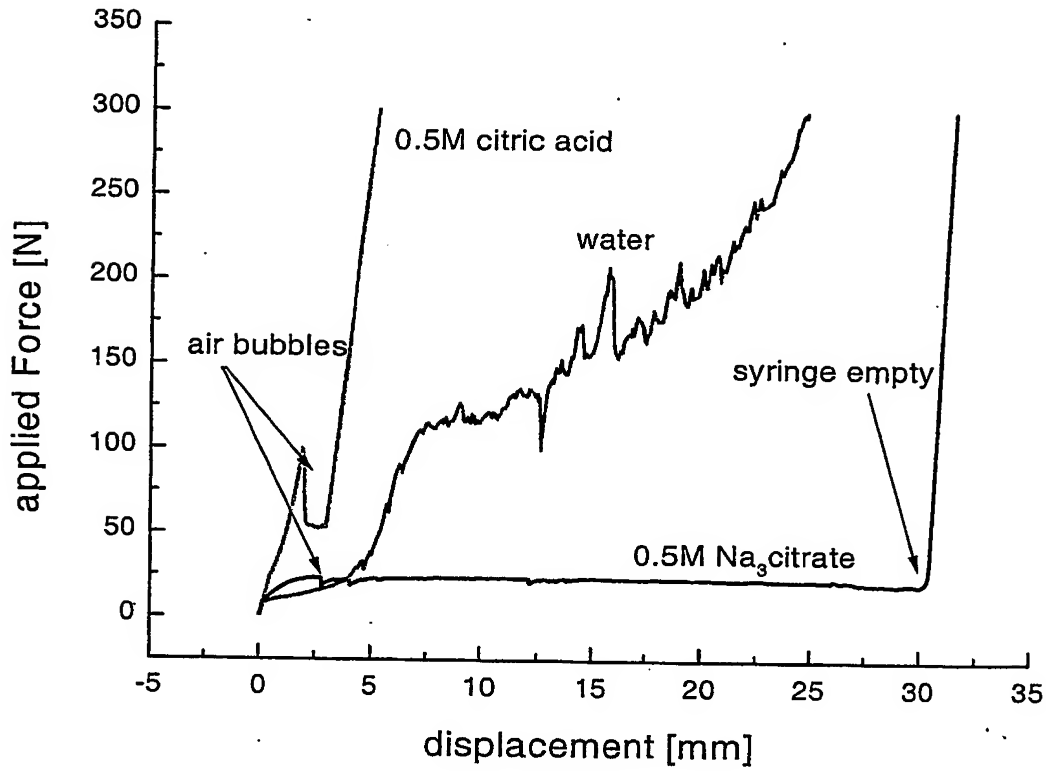
The invention is equally applicable to acidic setting cements. To demonstrate this, the injectability of the above cement using trisodium citrate as the liquid

component was compared with the same cement using citric acid. The proportion of injected cement was determined from the mass of cement remaining in a syringe having a 1 mm bore needle after injecting at a force of 300 N. The results are shown in Table 7 below. Injectability is improved using increasing concentrations of citric acid. Sodium citrate has the opposite effect, with the cement being virtually impossible to inject at 1M sodium citrate.

Table 7 Injectability of acidic setting cement solutions

Additive	P:L	Proportion Injected (wt%)
0.5 M Sodium citrate	3.3	51 ± 11.0
	4.0	1.37 ± 0.2
	4.5	NI
	5.0	NI
1 M Sodium citrate	3.3	1.6 ± 0.9
	4	NI
	4.5	NI
	5	NI
0.5 M Citric acid	3.3	23.6 ± 5.2
	4	2.1 ± 1.1
	4.5	NI
	5	NI
1 M Citric acid	3.3	79.7 ± 1.5
	4	76.3 ± 12.5
	4.5	9.3 ± 0.9
	5	NI

NI = not injectable


0.5M citric acid
water
air bubbles
syringe empty
0.5M Na3citrate
applied Force [N]
displacement [mm]
350
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